can play permissive or suppressive roles in determining the magnitude of SNS stress reactivity[2]. Because HPA axis functionality can precede and inform the nature of the sympathetic stress response, incorporating preceding levels of available cortisol *in situ* during moments of emotional strain may help to better calibrate measurements of SNS reactivity in dysphoric individuals.

Moreover, it has been demonstrated that the doctrine of reciprocal antagonism between the PNS and SNS – the notion that more of one inherently means less of the other – does not universally hold[6]. This conclusion dictates that the two systems can exhibit concurrent and interactive behavior and should be measured and modeled as separate and distinct dimensions. A systems approach to stress responsiveness may help to better define and measure the individual components.

However, methodological challenges remain regarding the measurement and timing of different system components. The cascade of HPA axis hormonal actions has been well documented, with peak effects following roughly 20 min after stress exposure[2]. Meanwhile, PNS effects such as vagal withdrawal can operate on a scale of milliseconds to seconds, and SNS effects typically take place on a scale of seconds to minutes. We propose that research into autonomic functioning in human subjects should be pursued via time series analysis of electrophysiological measurements.

Common inputs such as respiratory sinus arrhythmia, pre-ejection period, and heart rate can be binned in epochs as small as 30 sec. Thus, data collection periods as short as an hour can produce time series of 120 observations. Time series analyses such as vector-autoregression and network analysis can model the relationships between system components. Moreover, ambulatory technologies exist allowing researchers to capture autonomic functioning in emotionally salient scenarios during an individual's day-to-day life.

Measures such as pre-ejection period require academic-research-grade equipment and expertly placed electrodes. However, innovations in mobile assaying of salivary measures could yield ambulatory measurements of SNS markers such as salivary alpha-amylase. Additionally, one could foresee the development of a fingerstick system for capillary blood measurement of catecholamines akin to blood glucose monitoring systems. It has been shown that reliable measurements of catecholamines can be derived from as little as 100 μL of capillary blood[7].

Understanding the role of the SNS in the treatment of depression may be important for patients' psychological and physical health. As noted above, depressed individuals have been shown to have significantly decreased parasympathetic cardiac regulation, and depression has long been associated with an increased incidence of coronary heart disease[1,5]. Although the evidence for sympathetic predominance in depressed patients has been equivocal, there is some evidence that antidepressant medications may affect this predominance[8]. Of note, one study has found that cognitive behavioral treatment may increase heart rate variability[9]. Clearly, more work is needed to understand the effects of psychotherapy and antidepressant medications on the SNS and sympathetic cardiac control.

Finally, we noted at the outset the likely existence of heterogeneous subpopulations of depressed individuals, some of whom may experience elevations in sympathetic arousal and some may not. It follows that individuals could exhibit more complex individual differences in the calibration of stress responsivity among cognitive, affective and physiological system components.

From this perspective, the SNS could play a primary role in driving phenomenological and physiological consequences for some individuals. For instance, during the transduction of cognitive-emotional stimuli into physiological responses, an adrenergic gain factor might serve to amplify moderate signals into more robust responses. In a time series context, competing directional models of SNS arousal, subjective affect, and cognitive appraisal could be tested. Moreover, such evaluations could be carried out on a person-by-person basis.

The SNS plays a calibrating role, exerting effects in response to shifting external demands and emotional conditions. It may be more fruitful to examine these dynamic, time-varying relationships with other stress-response systems, rather than mean group differences.

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1. Carney RM, Freedland KE, Veith RC. Psychosom Med 2005;67:S29-33.
2. Sapolsky RM, Romero LM, Munck AU. Endocrine Rev 2000;21:55-89.
3. Disner SG, Beevers CG, Haigh EA et al. Nat Rev Neurosci 2011;12:467-77.
4. Keller J, Gomez R, Williams G et al. Mol Psychiatry 2017;22:527-36.
5. Kemp AH, Quintana DS, Gray MA et al. Biol Psychiatry 2010;67:1067-74.
6. Berntson GG, Cacioppo JT, Quigley KS. Psychol Rev 1991;98:459.
7. Baumgartner H, Ritsch R, Luz O et al. Pediatr Res 1992;31:579-82.
8. Koschke M, Boettger MK, Schulz S et al. Psychosom Med 2009;71:852-60.
9. Carney RM, Freedland KE, Stein PK et al. Psychosom Med 2000;62:639-47.

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Cardiac vagal tone: a neurophysiological mechanism that evolved in mammals to dampen threat reactions and promote sociality

The evolutionary journey from asocial reptiles to social mammals is highlighted by a reorganized autonomic nervous system with unique structural and functional changes in the vagus. These changes enable mammals to suppress defensive strategies in order to support and express sociality. The product of this transition is an autonomic nervous system with capacities to self-calm, to socially engage others, and to mitigate threat reactions in ourselves and others through social cues.

For mammals, whose survival is dependent on their ability to cooperate, to connect, and to co-regulate, the ancient defense programs dependent on sympathetic activation supporting fight/flight behaviors, and vagal activation supporting death feigning, had to be harnessed and repurposed. This process resulted in a reorganized brainstem area, the ventral vagal complex, from which a unique branch of the vagus nerve enabled the expression of several uniquely mammalian features, including the ability to calm and to signal safety. Thus, sociality became embedded within specific neurobiological processes that had capabilities to mitigate threat and support mental and physical health. When this "calming" system is disrupted, prominent markers of chronic stress and core features shared by several psychiatric conditions are expressed (e.g., flat facial affect, poor vocal prosody, hypervigilance, hyperreactivity, auditory and visual hypersensitivities).

Anatomically, this vagal pathway is myelinated and originates in the brainstem structure called nucleus ambiguus. It provides the primary vagal regulation of organs above the diaphragm. This is distinct from the vagal pathways originating in the dorsal vagus nucleus, which are unmyelinated and provide the primary vagal regulation of organs below the diaphragm. The ventral vagal complex also regulates the striated muscles of the face and head and is greatly influenced by afferent pathways traveling through the vagus, trigeminal and facial nerves. Thus, in mammals, the brainstem areas regulating the heart and bronchi are interconnected with the areas regulating ingestion, facial expression, listening, breathing and vocalizations, to form an integrated social engagement system. In fact, intonations of vocalizations are mediated by the vagus, enabling prosodic features of voice to convey a relatively accurate index of vagal regulation of the heart[1].

Following the work of Jackson[2], the polyvagal theory[3] assumes a phylogenetic hierarchy in which the newer circuits inhibit the older. Thus, when the ventral vagus and the social engagement system are dampened or go offline, which frequently is observed during chronic stress and in response to threat, the autonomic nervous system moves into a sympathetic state that supports mobilization (e.g., fight/flight). If this functional shift in state does not lead to a positive outcome, then the autonomic nervous system may abruptly shut down via the dorsal vagal circuit (e.g., syncope, death feigning).

Jackson described this process of sequentially disinhibiting older structures as *dissolution* or evolution in reverse. He used dissolution to explain the consequence of brain damage and disease, while polyvagal theory applies the principle to adaptive autonomic reactions to cues of threat, which may be reversible by cues of safety. In the realm of mental health, loss of access to the ventral vagus may be a product of chronic threat or a measurable core feature of several psychiatric disorders (e.g., post-traumatic stress disorder, PTSD), developmental disabilities (e.g., autism, Prader Willi syndrome), and disabling chronic pain.

To survive, mammalian offspring must initially nurse as the primary mode of ingesting food. To nurse the infant must suck, a process dependent on a brainstem circuit involving the ventral vagal complex. Survival is dependent on the infant's nervous system efficiently and effectively coordinating suck-swallow-breathe-vocalize behaviors with vagal regulation of the heart through the ventral vagal pathways originating in the nucleus ambiguus. Through maturation and socialization, this "ingestive" circuit provides the structural neural platform (i.e., social engagement system) for sociality and co-regulation as major mediators to optimize homeostatic function leading to health, growth and restoration.

In mammals, there is a dependency between reactions to contextual cues and the function of this circuit. Cues of threat may disrupt, while cues of safety may enhance function. The sensory branches of the facial and trigeminal nerves provide major input into the ventral vagal complex. Functionally, changes in the state of this circuit, through the process of dissolution, will either "disinhibit" phylogenetically older autonomic circuits to support defense (e.g., predator, disease, physical injury) or inform all aspects of the autonomic nervous system, including the enteric system[4], to optimize homeostatic function.

Polyvagal theory introduces "neuroception", a neural process that evaluates risk and safety and reflexively triggers shifts in autonomic state without requiring conscious awareness. This reflexive process, distinct from perception, detects environmental and visceral features that are safe, dangerous or life-threatening[5]. Although many vertebrates have a capacity to detect pain and threat, mammals repurposed the neuroception capacity of their reptilian ancestors to not only react instantaneously to threat, but also to calm instantaneously to cues of safety.

It is this latter feature that enables mammals to downregulate defensive strategies to promote sociality by enabling psychological and physical proximity without the consequences of injury. It is this calming mechanism that adaptively adjusts the central regulation of autonomic function to dampen sympathetic activation and to protect the oxygen-dependent central nervous system, especially the cortex, from the metabolically conservative defensive reactions of the dorsal vagal complex (e.g., syncope, diarrhea).

This potential to calm autonomic state via the social engagement system is compromised in many psychiatric conditions, and leads to a variety of autonomic dependent comorbidities, including irritable bowel syndrome, migraine and fibromyalgia. However, being a common feature of several disorders limits the potential utility of measures of ventral vagal function in differential diagnoses, although it would highlight the potential of recruiting the ventral vagal pathway as a portal for treatment via technologies (e.g., vagal nerve stimulation).

Our research documents that the quantification of the respiratory-related component of heart rate variability, known as respiratory sinus arrhythmia, provides a sensitive metric of the ventral vagus function (i.e., cardiac vagal tone)[6]. Applications of our method confirmed that respiratory sinus arrhythmia was even more sensitive than the assumed "gold standard" of cardiac vagal tone (i.e., changes in heart rate in response to vagal blockade).

Respiratory sinus arrhythmia is a physiological phenomenon with an identifiable underlying neural mechanism reflecting ventral vagal control of the heart. With an accurate measure of ventral vagal function, there is the possibility to monitor autonomic adjustments to threat and safety. From a clinical perspective, the ability to monitor dampened vagal regulation would provide insight

into understanding the mechanisms underlying clinical features. For example, chronic stress, clinical depression, or a life-threatening traumatic experience that may lead to PTSD could profoundly dampen ventral vagal regulation of the heart and the structures regulated by ventral vagal complex constituting the social engagement system[7,8].

Disrupting the brainstem locus of social engagement system would functionally impair social communication and co-regulation by reducing vocal prosody and facial affect, and, through the loss of neural tone to the middle ear muscles, influence auditory processing by inducing hypersensitivity to low frequency background sounds and hyposensitivity to voice. In concert with these changes, brainstem communication with higher brain structures would impair cognitive function and affect regulation, while supporting the defense strategies of fight or flight or shutdown (e.g., syncope, dissociation).

Monitoring ventral vagal function may provide an objective neurophysiological marker of clinical improvement[9].

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1. Porges SW, Lewis GF. Handb Behav Neurosci 2010;19:255-64.
2. Jackson JH. BMJ 1884;1:703-7.
3. Porges SW. Psychophysiology 1995;32:301-18.
4. Kolacz J, Porges SW. Front Med 2018;5:145.
5. Porges SW. Ann NY Acad Sci 2003;1008:31-47.
6. Lewis GF, Furman SA, McCool MF et al. Biol Psychol 2012;89:349-64.
7. Hage B, Britton B, Daniels D et al. World J Biol Psychiatry 2019;20:359-67.
8. Fanning J, Silfer JL, Liu H et al. J Behav Med 2020;43:308-17.
9. Porges SW, Macellaio M, Stanfill SD et al. Int J Psychophysiol 2013;88:261-70.

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Psychiatric comorbidity in immune-mediated inflammatory diseases

Chronic immune-mediated inflammatory diseases (IMIDs) are a group of conditions characterized by immune dysregulation and aberrant organ system inflammation. Common examples of these conditions include rheumatoid arthritis, inflammatory bowel disease (including Crohn's disease and ulcerative colitis) and multiple sclerosis. Although these conditions affect different organ systems, they are all characterized by recurrent relapses and potentially debilitating disease progression.

Collectively, IMIDs affect more than 1 in 20 people worldwide, and substantially burden affected persons, their families and societies. The adverse impacts of IMIDs include symptoms such as pain and fatigue, impairments in relationships and social participation, loss of employment, increased health care utilization, and reduced life expectancy. Comorbid conditions are common in people with IMIDs and also contribute substantially to their burden.

Comorbid psychiatric disorders, including depression, anxiety disorders and bipolar disorder, are of particular interest. A growing body of evidence indicates that the incidence and prevalence of psychiatric disorders are elevated in persons with IMIDs as compared to the general population. For example, a population-based cohort of persons with rheumatoid arthritis, inflammatory bowel disease or multiple sclerosis had an elevated incidence of depression (incidence rate ratio, IRR=1.71; 95% CI: 1.64-1.79), anxiety (IRR=1.34; 95% CI: 1.29-1.40), bipolar disorder (IRR=1.68; 95% CI: 1.52-1.85) and schizophrenia (IRR=1.32; 95% CI: 1.03-1.69) compared to age-, sex- and geographically-matched controls[1].

The association between IMIDs and psychiatric disorders appears to be bidirectional, and the increased incidence of psychiatric disorders is not simply due to the challenges of living with a chronic disease. In a population-based study from Denmark involving 1,016,519 individuals, those with depression had a significantly higher risk of developing any IMID in the subsequent 11 years than individuals without depression[2]. In a population-based study from Canada, individuals with rheumatoid arthritis, inflammatory bowel disease or multiple sclerosis had an increased incidence of any psychiatric disorder, including depression, anxiety, bipolar disorder and schizophrenia, for 8-10 years prior to the diagnosis of their IMID, even after accounting for sociodemographic factors and number of physician visits[3].

Broadly, two health conditions may be comorbid (co-occur) for several reasons. Chance alone may account for comorbidity. Surveillance bias may also occur, wherein a person affected by one chronic health condition uses more health care services and consequently is more likely to get diagnosed with a second condition. Furthermore, conditions may co-occur due to "true etiologic mechanisms". These mechanisms may include common genetic or environmental factors, or direct causation of the second condition by the first one. Finally, both conditions could be caused by an unrecognized third condition.

Epidemiological and biological evidence suggests that IMIDs and psychiatric disorders are comorbid due to "true etiologic mechanisms". In a cohort of 5,727,655 individuals, incident depression was associated with an increased risk of incident Crohn's disease (hazard ratio, HR=2.11; 95% CI: 1.65-2.70) and ulcerative colitis (HR=2.23; 95% CI: 1.92-2.60) after adjusting for age, sex, socioeconomic status, comorbid conditions, smoking status and use of antidepressants[4]. Notably, treatment with antidepressants was protective of developing Crohn's disease or ulcerative colitis among individuals with depression.

The role of inflammation and immune dysregulation in IMIDs is well-recognized. Emerging evidence is highlighting the importance of immune dysfunction in psychiatric disorders as well, including depression, bipolar disorder, schizophrenia and anxiety disorders[5]. These latter disorders are associated with dysregulation of T cell function and pro-inflammatory cytokines, including interleukin-6 (IL-6), IL-2 receptor, IL-1β, IL-17A, and